

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



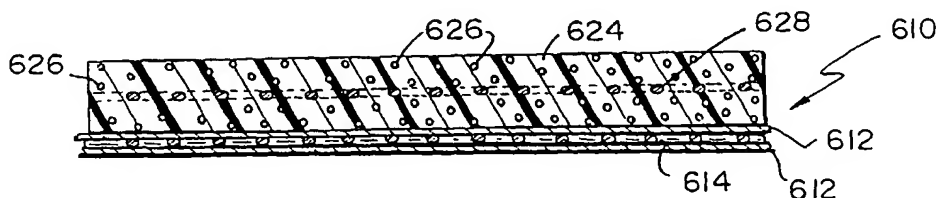
(43) International Publication Date
30 January 2003 (30.01.2003)

PCT

(10) International Publication Number
WO 03/007847 A1

- (51) International Patent Classification⁷: **A61F 2/02**
- (21) International Application Number: PCT/US02/22364
- (22) International Filing Date: 15 July 2002 (15.07.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/305,786 16 July 2001 (16.07.2001) US
09/918,116 30 July 2001 (30.07.2001) US
10/172,347 14 June 2002 (14.06.2002) US
- (71) Applicant (for all designated States except US): **DEPUY PRODUCTS, INC.** [US/US]; 700 Orthopaedic Drive, Warsaw, IN 46581 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **BROWN, Laura, Jean** [US/US]; 14 Gary Drive, Hamilton Square, NJ 08690 (US). **CHUN, Iksoo** [KR/US]; 6 Redwood Terrace, Flemington, NJ 08822 (US). **DHANARAJ, Sridevi** [IN/US]; 3 Roderer Drive, Raritan, NJ 08869 (US). **MALAVIYA, Prasanna** [IN/US]; 3610 Winterfield Run, Fort Wayne, IN 46804 (US). **MELICAN, Mora, C.** [US/US]; 2701 Johnson Circle, Bridgewater, NJ 08807 (US). **REZANIA, Alireza** [IR/US]; 5 Dewitt Lane, Hillsborough, NJ 08844 (US). **ZHANG, Li** [CN/US]; 316 White Pine Circle, Laurenceville, NJ 08648 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: HYBRID BIOLOGIC-SYNTHETIC BIOABSORABLE SCAFFOLDS



(57) Abstract: A bioprosthesis device(610) is provided for soft tissue attachment, reinforcement, and or reconstruction. The device (610) comprises a naturally occurring extracellular matrix portion (612) and a three-dimensional synthetic portion (624). In illustrated embodiments, the naturally occurring extracellular matrix portion (612) comprises layers of small intestine submucosa, and the three-dimensional synthetic portion comprises a foam or a three-dimensional mesh, textile or felt.

WO 03/007847 A1

B30

HYBRID BIOLOGIC-SYNTHETIC BIOABSORABLE SCAFFOLDS

CROSS REFERENCE TO RELATED APPLICATIONS

Cross reference is made to copending U.S. patent applications Serial
5 No. XX/XXX,XXX entitled "Meniscus Regeneration Device and Method" (Attorney
Docket No. 265280-71141, DEP-745); Serial No. XX/XXX,XXX entitled "Devices
from Naturally Occurring Biologically Derived Materials" (Attorney Docket No.
265280-71142, DEP-748); Serial No. XX/XXX,XXX entitled "Cartilage Repair
Apparatus and Method" (Attorney Docket No. 265280-71143, DEP-749); Serial No.
10 XX/XXX,XXX entitled "Unitary Surgical Device and Method" (Attorney Docket No.
DEP-750); Serial No. XX/XXX,XXX entitled "Hybrid Biologic/Synthetic Porous
Extracellular Matrix Scaffolds" (Attorney Docket No. 265280-71144, DEP-751);
Serial No. XX/XXX,XXX entitled "Cartilage Repair and Regeneration Device and
Method" (Attorney Docket No. 265280-71145, DEP-752); Serial No. XX/XXX,XXX
15 entitled "Porous Extracellular Matrix Scaffold and Method" (Attorney Docket No.
265280-71146, DEP-747); Serial No. XX/XXX,XXX entitled "Cartilage Repair and
Regeneration Scaffolds and Method" (Attorney Docket No. 265280-71180, DEP-
763); and Serial No. XX/XXX,XXX entitled "Porous Delivery Scaffold and Method"
(Attorney Docket No. 265280-71207, DEP-762), each of which is assigned to the
20 same assignee as the present application, each of which is filed concurrently herewith,
and each of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to bioprosthesis and particularly to the
25 use of bioprosthesis for the repair and replacement of connective tissue. More
particularly, the present invention relates to the use of a composite bioprosthesis
device made up of a synthetic portion and heterologous animal tissue.

BACKGROUND AND SUMMARY OF THE INVENTION

30 Currently there are multiple patents and publications which describe in
detail the characteristics and properties of small intestine submucosa (SIS). See, for
example, U.S. Patent Nos. 4,352,463, 4,902,508, 4,956,179, 5,281,422, 5,372,821,
5,445,833, 5,516,533, 5,573,784, 5,641,518, 5,645,860, 5,668,288, 5,695,998,

-2-

5,711,969, 5,730,933, 5,733,868, 5,753,267, 5,755,791, 5,762,966, 5,788,625, 5,866,414, 5,885,619, 5,922,028, 6,056,777, and WO 97/37613, incorporated herein by reference. SIS, in various forms, is commercially available from Cook Biotech Incorporated (Bloomington, IN). Further, U.S. Patent No. 4,400,833 to Kurland and PCT publication having International Publication Number WO 00/16822 provide information related to bioprosthetics and are also incorporated herein by reference.

It is also known to use naturally occurring extracellular matrices (ECMs) to provide a scaffold for tissue repair and regeneration. One such ECM is small intestine submucosa (SIS). SIS has been used to repair, support, and stabilize a wide variety of anatomical defects and traumatic injuries. Commercially available SIS material is derived from porcine small intestinal submucosa that remodels the qualities of its host when implanted in human soft tissues. Further, it is taught that the SIS material provides a natural matrix with a three-dimensional microstructure and biochemical composition that facilitates host cell proliferation and supports tissue remodeling. SIS products, such as Oasis material and Surgisis material, are commercially available from Cook Biotech, Bloomington, IN.

An SIS product referred to as RESTORE Orthobiologic Implant is available from DePuy Orthopaedics, Inc. in Warsaw, Indiana. The DePuy product is described for use during rotator cuff surgery, and is provided as a resorbable framework that allows the rotator cuff tendon to regenerate itself. The RESTORE Implant is derived from porcine small intestine submucosa that has been cleaned, disinfected, and sterilized. Small intestine submucosa (SIS) has been described as a naturally occurring ECM composed primarily of collagenous proteins. Other biological molecules, such as growth factors, glycosaminoglycans, etc., have also been identified in SIS. See Hodde et al., Tissue Eng. 2(3): 209-217 (1996); Voytik-Harbin et al., J. Cell Biochem., 67:478-491 (1997); McPherson and Badylak, Tissue Eng., 4(1): 75-83 (1998); Hodde et al., Endothelium, 8(1):11-24 (2001); Hodde and Hiles, Wounds, 13(5): 195-201 (2001); Hurst and Bonner, J. Biomater. Sci. Polym. Ed., 12(11) 1267-1279 (2001); Hodde et al., Biomaterial, 23(8): 1841-1848 (2002); and Hodde, Tissue Eng., 8(2): 295-308 (2002), all of which are incorporated by reference herein. During seven years of preclinical testing in animals, there were no incidences of infection transmission from the implant to the host, and the RESTORE Implant has not decreased the systemic activity of the immune system. See Allman

-3-

et al., Transplant, 17(11): 1631-1640 (2001); Allman et al., Tissue Eng., 8(1): 53-62 (2002).

While small intestine submucosa is available, other sources of submucosa are known to be effective for tissue remodeling. These sources include, but are not limited to, stomach, bladder, alimentary, respiratory, or genital submucosa, or liver basement membrane. See, e.g., U.S. Patents Nos. 6,379,710, 6,171,344, 6,099,567, and 5,554,389, hereby incorporated by reference. Further, while SIS is most often porcine derived, it is known that these various submucosa materials may be derived from non-porcine sources, including bovine and ovine sources.

Additionally, the ECM material may also include partial layers of laminar muscularis mucosa, muscularis mucosae, lamina propria, stratum compactum and/or other tissue materials depending upon factors such as the source from which the ECM material was derived and the delamination procedure.

For the purposes of this invention, it is within the definition of a naturally occurring ECM to clean, delaminate, and/or comminute the ECM, or even to cross-link the collagen fibers within the ECM. It is also within the definition of naturally occurring ECM to fully or partially remove one or more sub-components of the naturally occurring ECM. However, it is not within the definition of a naturally occurring ECM to separate and purify the natural collagen or other components or sub-components of the ECM and reform a matrix material from the purified natural collagen or other components or sub-components of the ECM. While reference is made to SIS, it is understood that other naturally occurring ECMs (e.g., stomach, bladder, alimentary, respiratory, and genital submucosa, and liver basement membrane), whatever the source (e.g., bovine, porcine, ovine) are within the scope of this disclosure. Thus, in this application, the terms "naturally occurring extracellular matrix" or "naturally occurring ECM" are intended to refer to extracellular matrix material that has been cleaned, disinfected, sterilized, and optionally cross-linked. The terms "naturally occurring extracellular matrix" and "naturally occurring ECM" are also intended to include ECM foam material prepared as described in copending U.S. Patent Application Serial No. XX/XXX,XXX entitled "Porous Delivery Scaffold and Method" (Attorney Docket No. 265280-71207, DEP-762), filed concurrently herewith.

-4-

There are currently many ways in which various types of tissues such as ligaments and tendons, for example, are reinforced and/or reconstructed. Suturing the torn or ruptured ends of the tissue is one method of attempting to restore function to the injured tissue. Sutures may also be reinforced through the use of synthetic non-bioabsorbable or bioabsorbable materials. Autografting, where tissue is taken from another site on the patient's body, is another means of soft tissue reconstruction. Yet another means of repair or reconstruction can be achieved through allografting, where tissue from a donor of the same species is used. Still another means of repair or reconstruction of soft tissue is through xenografting in which tissue from a donor of a different species is used.

According to the present invention, a bioprosthetic device for soft tissue attachment, reinforcement, and/or reconstruction is provided. The bioprosthetic device comprises SIS or other ECM formed to include a tissue layer, and a synthetic portion coupled to the tissue layer. The tissue layer may also be dehydrated.

In one embodiment, the SIS portion of the bioprosthetic device includes a top tissue layer of SIS material and a bottom tissue layer of SIS material coupled to the top tissue layer. The synthetic portion of the bioprosthetic device includes a row of fibers positioned to lie between the top and bottom tissue layers of the SIS portion. The fibers are positioned to lie in a spaced-apart coplanar relation to one another along a length, L , of the SIS portion. The fibers are each formed to include a length L_2 , where L_2 is longer than L so that an outer end portion of each fiber extends beyond the SIS portion in order to anchor the bioprosthetic device to the surrounding soft tissue.

Illustratively, in another embodiment, the synthetic reinforcing portion of the bioprosthetic device includes a mesh member formed to define the same length, L , as the SIS portion, or may include a mesh member having a body portion coupled to the SIS portion and outer wing members coupled to the body portion and positioned to extend beyond the length, L , and a width, W , of the SIS portion in order to provide more material for anchoring the bioprosthetic device to the surrounding soft tissue.

The synthetic reinforcing portion of the device enhances the mechanical integrity of the construct in one (for fiber reinforcements) or two (for fiber or mesh reinforcements) dimensions. For the repair of tissues such as meniscal or

-5-

articular cartilage, or discs, integrity in three dimensions is desirable for the implant to withstand the shear forces that will be present after implantation. Thus, in one embodiment of the present application, the absorbable synthetic portion of the device is in a three-dimensional form, to provide mechanical strength in three dimensions.

- 5 The absorbable synthetic may be a fibrous nonwoven construct or a three-dimensional woven mesh, for example.

For the repair of certain other types of tissues such as tendons, ligaments, or fascia, tissue infiltration and repair in three dimensions is desirable, although three-dimensional enhanced mechanical integrity of the implant is not
10 necessary. Thus, another embodiment of this invention is a composite device comprised of an SIS portion and an absorbable synthetic foam. The absorbable synthetic foam, in one example, is made of a biocompatible polymer that has a degradation profile that exceeds that of the SIS portion of the device. In this case, the SIS portion of the device provides the initial suturability of the product, and the
15 synthetic foam provides an increased surface area in three dimensions for enhanced tissue infiltration. In a further embodiment, that synthetic foam is made of 65/35 polyglycolic acid/polycaprolactone, or 60/40 polylactic acid/polycaprolactone, or a . 50:50 mix of the two.

The ECM portion of the composite may be provided as a single,
20 hydrated sheet of SIS. Alternatively, the single sheet of SIS is lyophilized (freeze-dried). Such a treatment renders increased porosity to the SIS sheet, thereby enhancing its capacity for allowing tissue ingrowth. Additionally, this SIS portion may comprise multiple sheets of SIS that have been laminated together by mechanical pressure while hydrated. The laminated SIS assembly optionally further physically
25 cross-linked by partially or fully drying (down to less than 15% moisture content) under vacuum pressure. Alternatively, the laminated SIS assembly is lyophilized, instead of being vacuum dried, to increase its porosity. In still another embodiment, the SIS sheet or laminate is perforated by mechanical means, to create holes ranging, for example, from 1 mm to 1 cm. Another embodiment uses woven textiles of single
30 or multi-layer SIS strips that have been optionally vacuum dried or lyophilized, to create meshes having different-sized openings. The woven mesh SIS optionally is assembled while the SIS is still hydrated and then the whole assembly vacuum-dried

-6-

or lyophilized. Such a construct is suturable in the short term, and has the advantage of having a very open structure for tissue ingrowth over time.

The three-dimensional synthetic portion of the device is illustratively provided in the form of a fibrous nonwoven or foam material. The synthetic portion of the device preferably has interconnecting pores or voids to facilitate the transport of nutrients and/or invasion of cells into the scaffold. The interconnected voids range in size, for example, from about 20 to 400 microns, preferably 50 to 250 microns, and constitute about 70 to 95 percent of the total volume of the construct. The range of the void size in the construct can be manipulated by changing process steps during construct fabrication. The foam optionally may be formed around a reinforcing material, for example, a knitted mesh.

The synthetic reinforcing portion of the device is made of a fibrous matrix made, for example, of threads, yarns, nets, laces, felts, and nonwovens. An illustrated method of combining the bioabsorbable fibrous materials, e.g., fibers, to make the fibrous matrix for use in devices of the present invention is known to one skilled in the art as the wet lay process of forming nonwovens. The wet lay method has been described in "Nonwoven Textiles," by Radko Krcma, Textile Trade Press, Manchester, England, 1967 pages 175-176.

Alternatively, the synthetic reinforcing portion of the device is made of a three-dimensional mesh or textile. A preferred method of combining the bioabsorbable fibrous materials, e.g., fibers, to make the fibrous matrix for use in devices of the present invention is known to one skilled in the art as three-dimensional weaving or knitting. The three-dimensional weaving/knitting or braiding method has been described by several groups who have used the constructs for tissue engineering applications including Chen et al. in "Collagen Hybridization with Poly(L-Lactic Acid) Braid Promotes Ligament Cell Migration," Mater. Sci. Eng. C, 17(1-2), 95-99(2001), and Bercovy et al., in "Carbon-PLGA Prostheses for Ligament Reconstruction Experimental Basis and Short Term Results in Man," Clin. Orthop. Relat. Res., (196), 159-68(1985). Such a three-dimensional material can provide both reinforcement and three-dimensional form.

The synthetic reinforcing portion of the tissue implant of the present invention may include textiles with woven, knitted, warped knitted (i.e., lace-like), nonwoven, and braided structures. In an exemplary embodiment the reinforcing

-7-

component has a mesh-like structure. However, in any of the above structures, mechanical properties of the material can be altered by changing the density or texture of the material. The fibers used to make the reinforcing component can be for example, monofilaments, yarns, threads, braids, or bundles of fibers. These fibers can
5 be made of any biocompatible material, including bioabsorbable materials such as polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polydioxanone (PDO), trimethylene carbonate (TMC), polyvinyl alcohol (PVA), copolymers or blends thereof. In an exemplary embodiment, the fibers that comprise the nonwoven or three-dimensional mesh are formed of a polylactic acid and
10 polyglycolic acid copolymer at a 95:5 mole ratio.

The ECM and the synthetic three-dimensional portion are provided in layers. It is understood for the purposes of this invention that the term "coupled to" describes a relationship wherein a surface of one layer is in contact with a surface of another layer and the two surfaces are connected through mechanical or chemical
15 means, such as through lamination, cross-linking, diffusion of the material of one layer into interstices of the adjacent layer, stitching, and the like. "Sandwiched between" describes a relationship wherein a middle layer has a first surface in contact with a surface of an adjacent layer, and a second opposite-facing surface in contact with a surface of a second adjacent layer. Again, it is understood that the sandwiched
20 layers are connected through mechanical or chemical means. The synthetic reinforcing portion may be provided as individual fibers or as layers. The synthetic reinforcing portion may be imbedded within a foam layer, provided between two other layers that are otherwise coupled together, or may form a layer that is coupled to one or more adjacent layers.

25 While various applications are envisioned, the devices of the present invention are particularly well suited for attachment of soft tissue to metallic replacement parts, for example attachment of soft tissue to the metallic proximal tibia portion of a total knee replacement.

It is anticipated that the devices of the present invention can be
30 combined with one or more bioactive agents (in addition to those already present in naturally occurring ECM), one or more biologically derived agents or substances, one or more cell types, one or more biological lubricants, one or more biocompatible inorganic materials, one or more biocompatible synthetic polymers and one or more

-8-

biopolymers. Moreover, the devices of the present invention can be combined with devices containing such materials.

“Bioactive agents” include one or more of the following: chemotactic agents; therapeutic agents (e.g., antibiotics, steroidal and non-steroidal analgesics and anti-inflammatories, anti-rejection agents such as immunosuppressants and anti-cancer drugs); various proteins (e.g., short chain peptides, bone morphogenic proteins, glycoprotein and lipoprotein); cell attachment mediators; biologically active ligands; integrin binding sequence; ligands; various growth and/or differentiation agents (e.g., epidermal growth factor, IGF-I, IGF-II, TGF- β I-III, growth and differentiation factors, vascular endothelial growth factors, fibroblast growth factors, platelet derived growth factors, insulin derived growth factor and transforming growth factors, parathyroid hormone, parathyroid hormone related peptide, bFGF; TGF β superfamily factors; BMP-2; BMP-4; BMP-6; BMP-12; sonic hedgehog; GDF5; GDF6; GDF8; PDGF); small molecules that affect the upregulation of specific growth factors; tenascin-C; hyaluronic acid; chondroitin sulfate; fibronectin; decorin; thromboelastin; thrombin-derived peptides; heparin-binding domains; heparin; heparin sulfate; DNA fragments and DNA plasmids. If other such substances have therapeutic value in the orthopaedic field, it is anticipated that at least some of these substances will have use in the present invention, and such substances should be included in the meaning of “bioactive agent” and “bioactive agents” unless expressly limited otherwise.

“Biologically derived agents” include one or more of the following: bone (autograft, allograft, and xenograft) and derivatives of bone; cartilage (autograft, allograft, and xenograft), including, for example, meniscal tissue, and derivatives; ligament (autograft, allograft, and xenograft) and derivatives; derivatives of intestinal tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of stomach tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of bladder tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of alimentary tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of respiratory tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of genital tissue (autograft, allograft, and xenograft), including for example submucosa; derivatives of liver tissue (autograft, allograft, and xenograft), including for example liver basement membrane; derivatives of skin

-9-

tissue; platelet rich plasma (PRP), platelet poor plasma, bone marrow aspirate, demineralized bone matrix, insulin derived growth factor, whole blood, fibrin and blood clot. Purified ECM and other collagen sources are also intended to be included within "biologically derived agents." If other such substances have therapeutic value in the orthopaedic field, it is anticipated that at least some of these substances will have use in the present invention, and such substances should be included in the meaning of "biologically derived agent" and "biologically derived agents" unless expressly limited otherwise.

"Biologically derived agents" also include bioremodelable collagenous tissue matrices. The expressions "bioremodelable collagenous tissue matrix" and "naturally occurring bioremodelable collagenous tissue matrix" include matrices derived from native tissue selected from the group consisting of skin, artery, vein, pericardium, heart valve, dura mater, ligament, bone, cartilage, bladder, liver, stomach, fascia and intestine, tendon, whatever the source. Although "naturally occurring bioremodelable collagenous tissue matrix" is intended to refer to matrix material that has been cleaned, processed, sterilized, and optionally cross-linked, it is not within the definition of a naturally occurring bioremodelable collagenous tissue matrix to purify the natural fibers and reform a matrix material from purified natural fibers. The term "bioremodelable collagenous tissue matrices" includes "extracellular matrices" within its definition.

"Cells" include one or more of the following: chondrocytes; fibrochondrocytes; osteocytes; osteoblasts; osteoclasts; synoviocytes; bone marrow cells; mesenchymal cells; stromal cells; stem cells; embryonic stem cells; precursor cells derived from adipose tissue; peripheral blood progenitor cells; stem cells isolated from adult tissue; genetically transformed cells; a combination of chondrocytes and other cells; a combination of osteocytes and other cells; a combination of synoviocytes and other cells; a combination of bone marrow cells and other cells; a combination of mesenchymal cells and other cells; a combination of stromal cells and other cells; a combination of stem cells and other cells; a combination of embryonic stem cells and other cells; a combination of precursor cells isolated from adult tissue and other cells; a combination of peripheral blood progenitor cells and other cells; a combination of stem cells isolated from adult tissue and other cells; and a combination of genetically transformed cells and other cells. If other cells are found

-10-

to have therapeutic value in the orthopaedic field, it is anticipated that at least some of these cells will have use in the present invention, and such cells should be included within the meaning of "cell" and "cells" unless expressly limited otherwise.

Illustratively, in one example of embodiments that are to be seeded with living cells such as chondrocytes, a sterilized implant may be subsequently seeded with living cells and packaged in an appropriate medium for the cell type used. For example, a cell culture medium comprising Dulbecco's Modified Eagles Medium (DMEM) can be used with standard additives such as non-essential amino acids, glucose, ascorbic acid, sodium pyruvate, fungicides, antibiotics, etc., in concentrations deemed appropriate for cell type, shipping conditions, etc.

"Biological lubricants" include: hyaluronic acid and its salts, such as sodium hyaluronate; glycosaminoglycans such as dermatan sulfate, heparan sulfate, chondroitin sulfate and keratan sulfate; synovial fluid and components of synovial fluid, including mucinous glycoproteins (e.g., lubricin), tribonectins, articular cartilage superficial zone proteins, surface-active phospholipids, lubricating glycoproteins I, II; vitronectin; and rooster comb hyaluronate. "Biological lubricant" is also intended to include commercial products such as ARTHREASETM high molecular weight sodium hyaluronate, available in Europe from DePuy International, Ltd. of Leeds, England, and manufactured by Bio-Technology General (Israel) Ltd., of Rehovot, Israel; SYNVISCO[®] Hylan G-F 20, manufactured by Biomatrix, Inc., of Ridgefield, New Jersey and distributed by Wyeth-Ayerst Pharmaceuticals of Philadelphia, Pennsylvania; HYLAGAN[®] sodium hyaluronate, available from Sanofi-Synthelabo, Inc., of New York, New York, manufactured by FIDIA S.p.A., of Padua, Italy; and HEALON[®] sodium hyaluronate, available from Pharmacia Corporation of Peapack, New Jersey in concentrations of 1%, 1.4% and 2.3% (for ophthalmologic uses). If other such substances have therapeutic value in the orthopaedic field, it is anticipated that at least some of these substances will have use in the present invention, and such substances should be included in the meaning of "biological lubricant" and "biological lubricants" unless expressly limited otherwise.

"Biocompatible polymers" is intended to include both synthetic polymers and biopolymers (e.g., collagen). Examples of biocompatible polymers include: polyesters of [alpha]-hydroxycarboxylic acids, such as poly(L-lactide) (PLLA) and polyglycolide (PGA); poly-p-dioxanone (PDS); polycaprolactone (PCL);

-11-

polyvinyl alcohol (PVA); polyethylene oxide (PEO); polymers disclosed in United States Pat. Nos. 6,333,029 and 6,355,699; and any other bioresorbable and biocompatible polymer, co-polymer or mixture of polymers or co-polymers that are utilized in the construction of prosthetic implants. In addition, as new biocompatible, 5 bioresorbable materials are developed, it is expected that at least some of them will be useful materials from which the anchors may be made. It should be understood that the above materials are identified by way of example only, and the present invention is not limited to any particular material unless expressly called for in the claims.

“Biocompatible inorganic materials” include materials such as 10 hydroxyapatite, all calcium phosphates, alpha-tricalcium phosphate, beta-tricalcium phosphate, calcium carbonate, barium carbonate, calcium sulfate, barium sulfate, polymorphs of calcium phosphate, sintered and non-sintered ceramic particles, and combinations of such materials. If other such substances have therapeutic value in the orthopaedic field, it is anticipated that at least some of these substances will have use 15 in the present invention, and such substances should be included in the meaning of “biocompatible inorganic material” and “biocompatible inorganic materials” unless expressly limited otherwise.

It is expected that various combinations of bioactive agents, biologically derived agents, cells, biological lubricants, biocompatible inorganic 20 materials, biocompatible polymers can be used with the devices of the present invention.

Thus, in one aspect of this invention a bioprosthetic device is provided comprising a layer of ECM material having a first surface, and a three-dimensional synthetic portion having a first surface, wherein the first surface of the ECM layer is 25 coupled to the first surface of the three-dimensional synthetic portion. The three-dimensional synthetic portion may be a fibrous material, illustratively selected from the group consisting of mesh, textile, and felt. Alternatively, the three-dimensional synthetic portion may be a synthetic foam.

In another aspect of this invention a prosthetic device is provided 30 comprising one or more layers of bioremodelable collageneous tissue matrices material coupled to one or more three-dimensional synthetic bodies to provide a three-dimensional composite for tissue attachment, reinforcement, or reconstruction.

-12-

In yet another aspect of this invention, a method for making a bioprosthetic device is provided, the method comprising the steps of providing a layer of ECM material having a first surface, placing a polymer solution in contact the first surface of the ECM material to make an assembly, wherein the polymer is selected to
5 form a foam upon lyophilization, and lyophilizing the assembly.

Additional features of the present invention will become apparent to those skilled in the art upon consideration of the following description of preferred embodiments of the invention exemplifying the best mode of carrying out the invention as presently perceived.

10

BRIEF DESCRIPTION OF THE DRAWINGS

The detailed description particularly refers to the accompanying figures in which:

Fig. 1 is a perspective view showing a composite bioprosthetic device
15 of the present invention formed to include a small intestinal submucosa (SIS) portion and a synthetic portion and showing the SIS portion including a top tissue layer of SIS material and a bottom tissue layer of SIS material and further showing the synthetic portion including a row of four fibers positioned to lie in coplanar relation to each other between the top and bottom tissue layers of the SIS portion and positioned to
20 run longitudinally along a length of the SIS portion and extend beyond a first and second end of the SIS portion in order to anchor the bioprosthetic device to surrounding soft tissue;

Fig. 2 is a perspective view similar to Fig. 1 showing an SIS portion of another bioprosthetic device of the present invention being formed to include a top
25 layer, a bottom layer, and two middle layers positioned to lie between the top and the bottom layers and a synthetic device being formed to include three rows of four fibers so that each row is positioned to lie between each of the adjacent tissue layers of the SIS portion so that each fiber is positioned to run longitudinally along a length, L, of the SIS portion;

30 Fig. 3 is a sectional view taken along line 3-3 of Fig. 2 showing the top, bottom, and middle tissue layers of the SIS portion and also showing the three rows of fibers of the synthetic portion of the bioprosthetic device;

-13-

Fig. 4 is a perspective view showing an SIS portion of yet another bioprosthetic device of the present invention being formed to include four tissue layers, similar to Fig. 2, and also showing a synthetic portion of the bioprosthetic device including a first row of multiple fibers positioned to lie between two tissue layers of the SIS portion along a length, L, of the SIS portion and a second row of multiple fibers positioned to lie between two other tissue layers of the SIS portion along a width, W, of the SIS portion;

Fig. 5 is an exploded perspective view of another bioprosthetic device of the present invention showing an SIS portion of the prosthetic device including top, bottom, and middle tissue layers and showing a synthetic portion including a first and a second mesh member positioned to lie between the top and middle tissue layers of and the middle and bottom tissue layers of the SIS portion, respectively;

Fig. 6 is a sectional view of the bioprosthetic device of Fig. 5 showing first and second mesh members "sandwiched" between the tissue layers of the SIS portion of the device;

Fig. 7 is a perspective view showing an SIS portion of another bioprosthetic device being formed to include a top and a bottom tissue layer and further showing a synthetic portion being formed to include a mesh member having a body portion positioned to lie between the top and bottom tissue layers and outer wing portions provided for anchoring the device to surrounding soft tissue;

Fig. 8 is a perspective view showing an SIS portion of yet another bioprosthetic device being formed to include a circularly shaped top and bottom tissue layers each having a diameter, D1, and further showing a synthetic portion of the device being formed to include a circular mesh member positioned to lie between the top and bottom tissue layers and having a diameter, D2, which is larger than D1 so that an outer rim portion of the mesh member is formed to extend beyond the top and bottom tissue layers for anchoring the bioprosthetic device to the host tissue during surgery;

Fig. 9 is a sectional view of a bioprosthetic device similar to the bioprosthetic device of Fig. 5, having two SIS layers, a reinforcing mesh material between the SIS layers, and a reinforced three-dimensional foam portion adjacent one of the SIS layers;

-14-

Fig. 10 is sectional view of another bioprosthetic device, wherein the SIS layer is sandwiched between two foam layers;

Fig. 11 is sectional view of another bioprosthetic device, wherein a foam layer is sandwiched between SIS layers;

5 Fig. 12 is a sectional view of another bioprosthetic device, wherein a three-dimensional synthetic layer is sandwiched between two SIS layers; and

Fig. 13 is a perspective view showing an SIS portion for use in another bioprosthetic device, wherein the SIS layer is made from weaving strips of SIS.

10 DETAILED DESCRIPTION OF THE DRAWINGS

A composite bioprosthetic device 10, as shown in Fig. 1, is provided for the purposes of soft tissue attachment, reinforcement, and/or reconstruction. Bioprosthetic device 10 includes a small intestinal submucosa (SIS) portion 12 and a synthetic portion 14. SIS portion 12 is provided to be absorbed into the body and replaced by host tissue. SIS portion 12 acts as a scaffold for tissue ingrowth and remodeling. Synthetic portion 14 of bioprosthetic device 10 provides additional initial mechanical strength to bioprosthetic device 10. Because device 10 includes SIS portion 12 and synthetic portion 14, bioprosthetic device 10 is provided with a differential in biodegradation and bioremodeling rates. Synthetic portion 14, for example, can be configured to degrade at a slower rate than SIS portion 12. Further, synthetic portion 14 may act as an anchor to couple bioprosthetic device 10 to the surrounding soft tissue (not shown) during surgery. Alternatively, the SIS portion may be sutured to couple the bioprosthetic device to the surrounding tissue.

SIS portion 12 of bioprosthetic device 10, as shown in Fig. 1, includes a top tissue layer 16 and a bottom tissue layer 18 coupled to top tissue layer 16 mechanically or through a dehydration process. Although top and bottom tissue layers 16, 18 are provided in bioprosthetic device 10 shown in Fig. 1, it is within the scope of this disclosure, as will be described in more detail later, to include SIS portions 12 having any number of tissue layers. It is also included within the scope of this disclosure to provide perforated tissue layers or any other physical configuration of SIS. See Figs. 2-4, for example. Further, it is within the scope of this disclosure to define top and bottom tissue layers 16, 18 as including multiple tissue layers each. In preferred embodiments, for example, top and bottom tissue layers 16, 18 each include

-15-

three to four layers of SIS tissue. SIS portion 12 further includes a first end 20, a second end 22 spaced-apart from first end 20, and sides 24 coupled to and positioned to lie between first and second ends 20, 22. A length, L, is defined as the distance between first end 20 and second end 22 and a width, W, is defined as the distance
5 between sides 24.

Synthetic portion 14 of bioprosthetic device 10 includes row 26 of four fibers 28, as shown in Fig. 1. It is within the scope of the disclosure to define fibers to include fibers or any fibrous material. Fibers 28 are positioned to lie along length L between top and bottom tissue layers 16, 18 and are further positioned to lie in
10 coplanar relation to one another. When making bioprosthetic device 10, fibers 28 of synthetic portion 14 are placed between top and bottom tissue layers 16, 18 prior to dehydration. Although row 26 of four fibers 28 is provided in bioprosthetic device 10 shown in Fig. 1, it is within the scope of this disclosure to include synthetic portions 14 formed to include any number of rows 26 having any number of fibers 28. It is
15 further within the scope of this disclosure to include fibers 28 made from bioabsorbable and non-bioabsorbable materials. For example, it is within the scope of this disclosure to include fibers 28 made from polylactic acid (PLA) or polyglycolic (PGA) acid, a combination of the two, Panacryl™ absorbable suture (Ethicon, Inc, Somerville, NJ), other bioabsorbable materials, nylon, polyethylene, Kevlar™,
20 Dacron™, PTFE, carbon fiber, or other non-bioabsorbable materials.

As shown in Fig. 1, each fiber 28 of bioprosthetic device 10 includes two outer end portions 30 a middle portion 32 coupled to and positioned to lie between outer end portions 30. Middle portion 32 is positioned to lie between top tissue layer 16 and bottom tissue layer 18 of SIS portion 12. Middle portion 32 of
25 fibers 28 helps to provide strength along length, L, of bioprosthetic device 10. One or more outer end portions 30 of fibers 28 can be used for anchoring bioprosthetic device 10 to surrounding soft tissue (not shown). The combination of SIS portion 12 and fibers 28 further provide bioprosthetic device 10 with differential biodegradation rates. For example, fibers 28 of synthetic portion 14 can be made to be non-
30 bioabsorbable or can be made with material which absorbs into the body at a slower rate than SIS portion 12. Uses for bioprosthetic device 10 shown in Fig. 1 include, but are not limited to, ligament or tendon repair.

-16-

An alternate bioprosthetic device 110 is shown in Figs. 2 and 3.

Bioprosthetic device 110 include an alternate SIS portion 112 of having top tissue layer 16, bottom tissue layer 18, and two middle tissue layers 115. Top, bottom, and middle tissue layers 16, 18, 115 include one or more layers of SIS tissue each. SIS portion 112, similar to SIS portion 12, also includes a first end 20, a second end 22 spaced-apart from first end 20, and sides 24. Bioprosthetic device 110 further includes an alternate synthetic portion 114 having three rows 26 of four fibers 28. One row 26 is positioned to lie between top tissue layer 16 and one of the middle tissue layers 115. Another row 26 is positioned to lie between the two middle tissue layers 115, and the final row 26 of fibers 28 is positioned to lie between another one of the middle tissue layers 115 and bottom tissue layer 16, as shown in Fig. 3. Fibers 28 of bioprosthetic device 110, similar to fibers 28 of bioprosthetic device 10, are positioned to lie along length, L, of SIS portion 112.

Although fibers 28 of bioprosthetic devices 10, 110 are positioned to lie along length, L, of each respective SIS portion 12, 112, it is within the scope of this disclosure to include a synthetic portion 214 of an alternate bioprosthetic device 210, as shown in Fig. 4, having multi-directional fibers 28 positioned to lie along a length, L, of an SIS portion 212 and along width, W, of SIS portion 212. Synthetic portion 214 of bioprosthetic device 210 includes a first row 226 having seventeen fibers 28 positioned to lie along length, L, of SIS portion 212. Synthetic portion 214 further includes a second row 227 having eighteen fibers 28 positioned to lie along width, W, of SIS portion 212 so that the fibers 28 of first row 226 and second row 227 are positioned to lie orthogonally with respect to each other. Although rows 226 and 227 are positioned to lie in orthogonal relation to one another, it is within the scope of this disclosure to include synthetic portion 214 having first and second rows 226 and 227 which lie at any angular relation to one another. It is also within the scope of this disclosure to include rows 226 and 227 each having any number of fibers 28.

Similar to bioprosthetic device 110 shown in Fig. 2, bioprosthetic device 210 includes a top tissue layer 216, a bottom tissue layer 218, and two middle tissue layers 215, positioned to lie between top and bottom tissue layers 216, 218. As mentioned before, top, bottom, and middle tissue layers 216, 218, 215 are each formed to include one or more layers of SIS tissue. Although SIS portion 212 of bioprosthetic device 210 is shown to include four tissue layers, it is within the scope

-17-

of the disclosure to include bioprosthetic device 210 having any number of tissue layers. As shown in Fig. 4, first row 226 is positioned to lie between top tissue layer 216 and one of the two middle tissue layers 215 positioned to lie adjacent to top tissue layer 216. Second row 227 is positioned to lie between the other middle tissue layer 215 and bottom tissue layer 218. It is within the scope of this disclosure, however, to include rows 226, 227 positioned to lie between any tissue layer of device 210.

Yet another bioprosthetic device 310 is shown in Figs. 5 and 6.

Bioprosthetic device 310 is similar to devices, 10, 110, and 210 and includes an SIS portion 312 having a top tissue layer 316, a bottom tissue layer 318, and a middle tissue layer 315 positioned to lie between top and bottom tissue layers 316, 318. Top, bottom, and middle tissue layers 316, 318, 315 each include one or more layers of SIS tissue. Bioprosthetic device 310 further includes a synthetic portion 314 including first mesh member 320 and second mesh member 322. It is within the scope of this disclosure to include any type of synthetic mesh member. For example, bioabsorbable and/or non-bioabsorbable mesh members 320, 322 made of either woven or nonwoven PGA and/or PLA mixtures are included within the scope of disclosure of this invention. First mesh member 320 is coupled to and positioned to lie between top tissue layer 316 and middle tissue layer 315 and second mesh member 322 is coupled to and positioned to lie between middle tissue layer 315 and bottom tissue layer 318, as shown in Figs. 5 and 6. Each of the first and second mesh members 320, 322 has a length, L, and a width, W, approximately equal to length, L, and width, W, of tissue layers 315, 316, 318, of SIS portion 312. It is understood that in some embodiments, it may be preferable for the mesh to be slightly smaller than the SIS portion.

In Fig. 5, second mesh member 322 is shown partially coated in comminuted SIS 340. Comminuted SIS may be used to fill the interstices of second mesh member 322 to provide a stronger device. Other means for reinforcing bioprosthetic device 10 may be employed, including suturing or tacking the various layers together. Further, while comminuted SIS is discussed with respect to the embodiment shown in Fig. 5, it is understood that comminuted SIS may be used to coat the mesh or fibers for any embodiment.

Another embodiment of the present invention includes a bioprosthetic device 410 having a synthetic portion 414 including a mesh member 420, as shown in

-18-

Fig. 7. Similar to the previously mentioned devices, bioprosthetic device 410 includes an SIS portion 412 having a top tissue layer 416 and a bottom tissue layer 418 coupled to top tissue layer 416. Top and bottom tissue layers 416, 418 each include one or more layers of SIS tissue. Mesh member 420 includes a central body portion (not shown) and outer wing portions 430, as shown in Fig. 7. Outer wing portions 430 are extensions of the central body portion. Although four outer wing portions 430 are shown in Fig. 7, it is within the scope of this disclosure to include a mesh member having a body portion and any number of wing portions 430 coupled to the body portion. The central body portion of mesh member 420 is formed to include a length and a width equal to length, L, and width, W, of SIS portion 412. The central body portion is coupled to and positioned to lie between top tissue layer 416 and bottom tissue layer 418 of SIS portion 420. Each wing portion 430 is coupled to the central body portion of mesh member 420 and is positioned to extend beyond the length, L, and width, W, of SIS portion 412, as shown in Fig. 7. As mentioned before, outer wing portions 430 are extensions of the central body portion. Wing portions 430 provide additional material for anchoring bioprosthetic device 410 to the surrounding soft tissue. Because outer wing portions 430 extend beyond central body portion of mesh member 420, mesh member 420 has a length and a width greater than length, L, and width, W, of SIS portion 412.

Yet another embodiment of the present invention is shown in Fig. 8 showing a bioprosthetic device 510 similar to bioprosthetic device 410, described above. Bioprosthetic device 510 includes an SIS portion 512 and a synthetic portion 514 coupled to SIS portion 512. SIS portion 512 includes a top tissue layer 516 which is circular in shape and a bottom tissue layer 518 which is also circular in shape. Each of the top and bottom tissue layers 516, 518 include one or more layers of SIS tissue. Top and bottom tissue layers 516, 518 each have a diameter, D1. The synthetic portion 514 of bioprosthetic device 510 includes a mesh member 520 coupled to and positioned to lie between top and bottom tissue layers 516, 518. Mesh member 520 is circular in shape and has a diameter, D2, which is greater than diameter, D1, of synthetic portion 512. Therefore, as shown in Fig. 8, an outer rim portion 530 of mesh member 520 is provided. Similar to outer wing portions 430 of bioprosthetic device 410, shown in Fig. 7, outer rim portion 530 of bioprosthetic

-19-

device 510 provides additional material for anchoring bioprosthetic device 510 to the surrounding soft tissue during surgery.

Fig. 9 shows a three-dimensional prosthetic device 610, having several SIS layers 612, a synthetic reinforcing material 614 positioned to lie between the SIS layers 612, and a three-dimensional synthetic portion 624. The SIS layer 612 may comprise any number of tissue layers. Furthermore, illustratively, if more than one layer is used, the layers may be laminated together. It is included within the scope of this disclosure to provide perforated tissue layers or any other physical configuration of SIS. As with the embodiments shown in Figs. 5-8, any number of SIS and reinforcing layers may be used, depending on the application.

Synthetic reinforcing material 614 illustratively comprises a two-dimensional fibrous matrix construct, as shown in Figs. 5-8, and may have the same length and width as the SIS layer, as shown in Fig. 5, may be slightly smaller, or may extend beyond the ends of the SIS layer, as shown in Figs. 7-8. Alternatively, synthetic reinforcing material may comprise a three-dimensional mesh, textile, felt, or other fibrous nonwoven construct, which may be shaped or formed for the particular application. The fibers comprise any biocompatible material, including PLA, PGA, PCL, PDO, TMC, PVA, or copolymers or blends thereof. In one example, mesh material is a 95:5 copolymer of PLA/PGA.

Three-dimensional synthetic portion 624 is a nonwoven material prepared to have numerous interconnecting pores or voids 626. Illustratively, the size of the voids may range from 20 to 400 microns. However, the size of the voids may be adjusted depending on the application, and the size may be manipulated by changing process steps during construction by altering freezing temperature, rate of temperature change and vacuum profile. Examples of various polymers that may be used for the foam, as well as various lyophilization profiles to control porosity, are described in U.S. Patent Nos. 6,333,029 and 6,355,699, hereby incorporated by reference. Optionally, three-dimensional synthetic portion 624 further comprises a synthetic reinforcing layer 628 embedded within the foam. Reinforcing layer 628 illustratively provides enhanced mechanical integrity to the three-dimensional synthetic portion. In an illustrated embodiment, a Vicryl knitted mesh is used. However, other reinforcing layers may be used.

-20-

Optionally, three-dimensional synthetic portion 624 may be a hybrid ECM/synthetic foam portion. In making such a foam, the polymer solution is mixed with a slurry of comminuted SIS prior to lyophilization. See copending U.S. Application No. XX/XXX,XXX entitled "Porous Delivery Scaffold and Method"

5 (Attorney Docket No. 265280-71207, DEP-762), hereby incorporated by reference.

Fig. 10 shows a bioprosthetic device 710 that is similar to that of Fig. 9. In Fig. 10, the SIS layer 712 is sandwiched between two three-dimensional synthetic portions 724, 730. Illustratively, both three-dimensional synthetic portions are foams, having voids 726. As shown, three-dimensional synthetic portion 724 has
10 a reinforcing mesh 728, while three-dimensional synthetic portion 730 does not have a reinforcing member. However, other arrangements are possible, and Fig. 11 shows an embodiment 810 where the SIS layer 812 is sandwiched between two three-dimensional synthetic portions 824, 830, neither of which has reinforcing members.

Fig. 12 shows another embodiment 910, wherein a single three-
15 dimensional synthetic portion 964 is sandwiched between two SIS layers 952, 953. As shown, three-dimensional synthetic portion 964 is a foam, with voids 966, but other three-dimensional synthetic portions may be used.

Fig. 13 shows a woven mesh 912 made from strips 928 of SIS. Fresh, lyophilized, or laminated strips of SIS may be cut into narrower strips and woven into
20 a mesh. The strips may be of any width, depending on the application, for example 0.1 to 20 mm, more particularly 1.0 mm wide strips. Optionally, the woven strips may be laminated together to provide enhanced mechanical support. The SIS woven mesh may be used as the SIS layer in any of the above embodiments. When used with the synthetic foams, if sufficient space is provided in the weaving, the foams will
25 form through the spaces within the mesh.

While the devices shown in Figs. 9-13 specific embodiments, it is understood that other arrangements are within the scope of this invention. For example, in Figs. 10-11, an SIS layer is sandwiched between two three-dimensional foam sections, with or without a reinforcing material embedded within the foam.
30 Additional reinforcing layers, as shown in Fig. 9 may be used with these embodiments. Similarly, when a single three-dimensional foam portion is sandwiched between two SIS layers, as in Fig. 12, a layer of reinforcing material may be used, depending upon the application. In still another embodiment, the reinforcing

-21-

portion may comprise a three-dimensional mesh or textile, and the three-dimensional foam portion may be omitted. It is also within the scope of this disclosure to further define the SIS portion to include sheets, perforated sheets, or any other physical configuration of SIS. Furthermore, the synthetic portion may comprise Prolene™ (Ethicon, Inc, Somerville, NJ) meshes and/or sutures, Vicryl™ (Ethicon, Inc, Somerville, NJ) meshes and/or sutures, Mersilene™ (Ethicon, Inc, Somerville, NJ) meshes, PDS II™ (Ethicon, Inc., Somerville, NJ) meshes or sutures, Panacryl™ (Ethicon, Inc., Somerville, NJ) meshes or sutures, and Monocryl™ meshes or sutures, for example. Additional two or three-dimensional meshes may be constructed for particular applications. Further it is within the scope of this disclosure to include bioprosthetic devices where the SIS portion includes any number of tissue layers and where multiple tissue layers are positioned to lie along each synthetic layer. The SIS layers may be dehydrated prior to or subsequent to assembly of the device. Further, any shape and/or orientation of the SIS portion and the synthetic portion of the bioprosthetic device is within the scope of this disclosure; Figs. 1-13 are merely examples of various embodiments of the present invention.

EXAMPLE 1

Sheets of clean, disinfected porcine SIS material were obtained as described in U.S. Patent No. 4,902,508 and 4,956,178. Ten strips, 3.5 inches wide and 6 inches long were cut. The strips were hydrated by placing in RO water, at room temperature, for 5 minutes.

To assemble the implant, five SIS strips were placed on top of each other, while ensuring no air bubbles were trapped between the strips. A knitted Panacryl™ mesh, 2 inches wide and 5 inches long, was placed centrally on the 5-layer thick SIS strip. The mesh had been pretreated to remove any traces of oil or other contaminants due to handling. This was done by a series of rinses, each 2 minutes long, in 100%, 90%, 80%, 70% ethanol (200 proof) in RO water, followed by a final 5 minute in RO water. Subsequently, a second 5-layer thick strip of SIS was assembled and placed to sandwich the mesh between the two SIS strips.

The implant was dried under vacuum pressure using a gel drier system (Model FB-GD-45, Fisher Scientific, Pittsburgh, PA) for 3 hours. The gel drier bed temperature was set at 30oC for the procedure. This drying procedure results in

-22-

“squeezing out” of the bulk water in the implant and also reduces the amount of bound water within the tissue, resulting in a final moisture of between 7%-8%. This process also results in a physical cross-linking between the laminates of SIS and between the mesh and adjacent SIS laminates.

5

EXAMPLE 2

This example describes the preparation of three-dimensional composite tissue implants incorporating a biodegradable SIS laminated sheet, a synthetic reinforcement in the form of a biodegradable mesh, and a synthetic degradable foam.

10

A solution of the polymer to be lyophilized to form the foam component was prepared in a four step process. A 95:5 weight ratio solution of 1,4-dioxane/(40/60 PCL/PLA) was made and poured into a flask. The flask was placed in a water bath, stirring at 60-70°C for 5 hrs. The solution was filtered using an extraction thimble, extra coarse porosity, type ASTM 170-220 (EC) and stored in

15

flasks.

A three-dimensional mesh material composed of a 95:5 copolymer of polylactic/polyglycolic acid (PLA/PGA) knitted mesh was rendered flat to control curling by using a compression molder at 80°C for 2 min. After preparing the mesh, 0.8-mm metal shims were placed at each end of a 4 X 4 inch aluminum mold, and the

20 mesh was sized to fit the mold. The synthetic mesh was then laid into the mold, covering both shims. Next, an SIS laminated sheet was placed over the mesh followed by additional shims to cover the edges of the SIS and synthetic mesh.

The polymer solution (40:60 PCL/PLA) was added into mold such that the solution covered the sheet of SIS as well as the mesh and reached a level of 3.0

25 mm in the mold.

The mold assembly then was placed on the shelf of the lyophilizer (Virtis, Gardiner, NY) and the freeze dry sequence begun. The freeze dry sequence used in this example was: 1) -17°C for 60 minutes; 2) -5°C for 60 minutes under vacuum of 100 mT; 3) 5°C for 60 minutes under vacuum of 20 mT; 4) 20°C for 60

30 minutes under vacuum of 20 mT.

After the cycle was completed, the mold assembly was taken out of the freeze drier and allowed to degas in a vacuum hood for 2 to 3 hours, and stored under nitrogen.

-23-

The resultant bioprosthetic device has a structure as illustrated in Fig.

9. The three-dimensional mesh provides both mechanical strength and three-dimensional structure to the resultant device. The foam may be shaped or sculpted for the particular application, and the mesh/SIS layers may be trimmed to fit. It is also
5 understood that the mold could be provided in the desired shape, reducing or obviating the need for sculpting or trimming.

EXAMPLE 3

- This example uses the process outlined in Example 2 to fabricate a
10 biodegradable composite scaffold of the present invention where the foam component is a 65:35 PGA/PCL copolymer.

EXAMPLE 4

- This example uses the process outlined in Example 2 to fabricate a
15 biodegradable composite scaffold of the present invention where the synthetic knitted mesh component is composed of 100% PDO.

EXAMPLE 5

- This example uses the process outlined in Example 2 to fabricate a
20 biodegradable composite scaffold of the present invention where in place of a three-dimensional mesh, the synthetic component is a nonwoven fibrous structure composed of either 100% PDO, 100% 90/10 PGA/PLA or a combination of the two.

EXAMPLE 6

- 25 This example uses the process outlined in Example 2 to fabricate a biodegradable composite scaffold of the present invention where the SIS component is soaked overnight in the polymer solution (5% wt 60/40 PLA/PCL in dioxane) prior to placement over the synthetic mesh. Enhanced lamination between the components was found when this additional soaking step was added to the process as evidenced by
30 a composite with a greater degree of handlability.

EXAMPLE 7

This example uses the process outlined in Example 2 to fabricate a biodegradable composite scaffold of the present invention where the SIS component is a single layer sheet rather than a laminated sheet.

5

EXAMPLE 8

This example uses the process outlined in Example 2 to fabricate a biodegradable composite scaffold of the present invention where the SIS laminated sheet is perforated with holes ranging from 1 mm - 1 cm. These perforations allow for enhanced penetration of the polymer solution through the SIS sheet.

10

EXAMPLE 9

This example uses the process outlined in Example 2 to fabricate a biodegradable composite scaffold of the present invention where the SIS reinforcing component is a "woven mesh" of laminated strips sandwiched between two layers of 60/40 PLA/PCL foam. Fig. 13 shows such a woven mesh. Fig. 11, wherein the SIS layer is a woven mesh of Fig. 13, illustrates the construct of this Example.

15

Although the invention has been described in detail with reference to certain preferred embodiments, variations and modifications exist within the scope and spirit of the invention as described and defined in the following claims.

20

-25-

CLAIMS:

1. A bioprosthetic device comprising
a layer of ECM material having a first surface, and
a three-dimensional synthetic portion having a first surface,
5 wherein the first surface of the ECM layer is coupled to the first
surface of the three-dimensional synthetic portion.
2. The bioprosthetic device of claim 1, wherein the ECM layer
comprises an SIS layer.
3. The bioprosthetic device of claim 2, wherein the SIS layer
10 comprises several SIS strips laminated together.
4. The bioprosthetic device of claim 3, wherein the laminated SIS
strips are perforated.
5. The bioprosthetic device of claim 2, wherein the SIS layer
comprises a woven mesh of strips of SIS.
- 15 6. The bioprosthetic device of claim 1, wherein the three-
dimensional portion comprises a fibrous material.
7. The bioprosthetic device of claim 6, wherein the fibrous
material is selected from the group consisting of mesh, textile, and felt.
8. The bioprosthetic device of claim 6, wherein the fibrous
20 material is a bioabsorbable material selected from the group consisting of PLA, PGA,
PCL, PDO, TMC, PVA, copolymers thereof, and blends thereof.
9. The bioprosthetic device of claim 1, wherein the three-
dimensional portion comprises a synthetic foam.
10. The bioprosthetic device of claim 9, wherein the synthetic foam
25 has voids in size from about 20 to 400 microns.
11. The bioprosthetic device of claim 10, wherein the voids
comprise about 70 to about 95 percent of the volume of the foam.
12. The bioprosthetic device of claim 9, wherein the ECM layer is
perforated, and the synthetic foam penetrates into the perforations in the ECM layer.
- 30 13. The bioprosthetic device of claim 9, further comprising
a second foam having a surface,

-26-

wherein the ECM layer comprises a second surface facing away from the first surface, and the surface of the second foam is coupled to the second surface of the ECM layer.

5 14. The bioprosthetic device of claim 9, further comprising
an additional ECM layer having a first surface,
and a synthetic reinforcing portion,

 wherein the ECM layer comprises a second surface facing away from
the first surface, the first surface of the second ECM layer is coupled to the second
surface, and the reinforcing portion is provided between the first and second ECM
10 layer.

 15. The bioprosthetic device of claim 14, wherein the reinforcing
portion is a three-dimensional mesh or textile.

 16. The bioprosthetic device of claim 9, wherein the synthetic foam
has a synthetic reinforcing layer embedded therein.

15 17. The bioprosthetic device of claim 9, further comprising a
second layer of ECM material having a first surface,
the synthetic foam comprises a second surface facing away from the
first surface, and

 wherein the first surface of the second ECM layer is coupled to the
20 second surface of the synthetic foam.

 18. The bioprosthetic device of claim 1, further comprising an
additional exogenous material selected from the group consisting of a bioactive agent,
a biologically derived agent, a cell, a biological lubricant, a biocompatible inorganic
material, and a biocompatible synthetic polymer.

25 19. A prosthetic device comprising one or more layers of
bioremodelable collageneous tissue matrix material coupled to one or more three-
dimensional synthetic bodies to provide a three-dimensional composite for tissue
attachment, reinforcement, or reconstruction.

 20. A method for making a bioprosthetic device, comprising the
30 steps of
providing a layer of ECM material having a first surface,

-27-

placing a polymer solution in contact the first surface of the ECM material to make an assembly, wherein the polymer is selected to form a foam upon lyophilization, and
lyophilizing the assembly.

5 21. The method of claim 20, wherein the ECM material comprises a second surface facing away from the first surface, and further comprising the step of
prior to the lyophilization step, placing a second polymer solution in contact with the second surface.

10 22. The method of claim 20, wherein the ECM material comprises a second surface facing away from the first surface, and further comprising the steps of

providing a second layer of ECM material having a first surface,
providing a reinforcing layer having a first surface and a second opposite-facing surface,

15 prior to the lyophilization step, placing the first surface of the reinforcing layer in contact with the second surface of the first ECM layer, and placing the second surface of the reinforcing layer in contact with the first surface of the second ECM layer.

20 23. The method of claim 20, wherein the ECM material comprises a plurality of SIS layers laminated together.

24. The method of claim 20, wherein the ECM material is perforated, and wherein the polymer solution diffuses into the perforations.

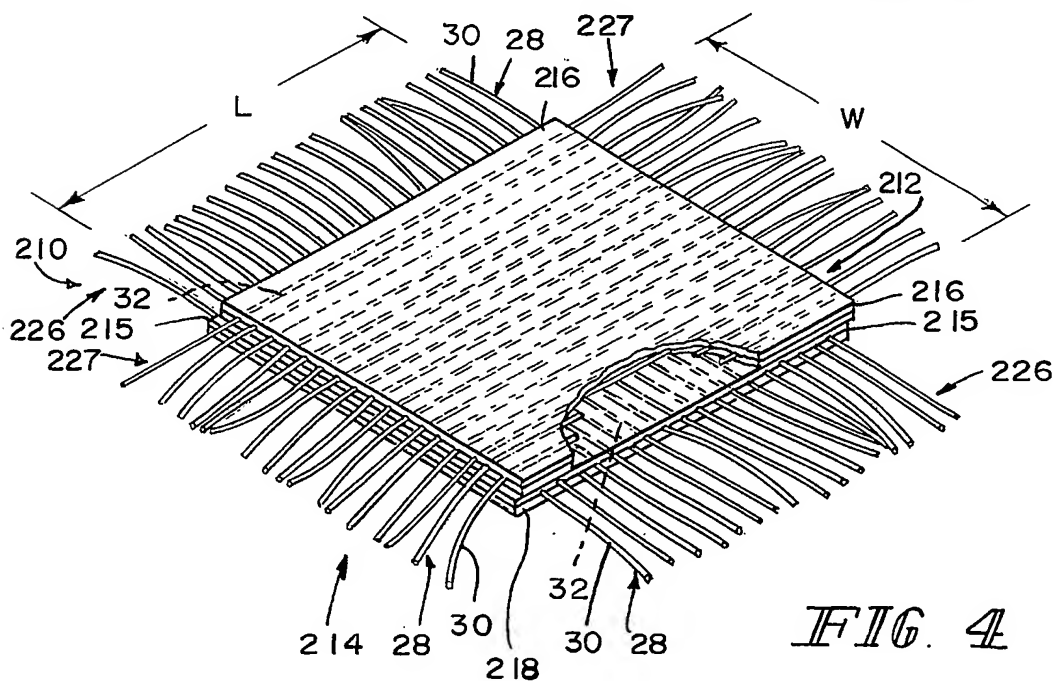
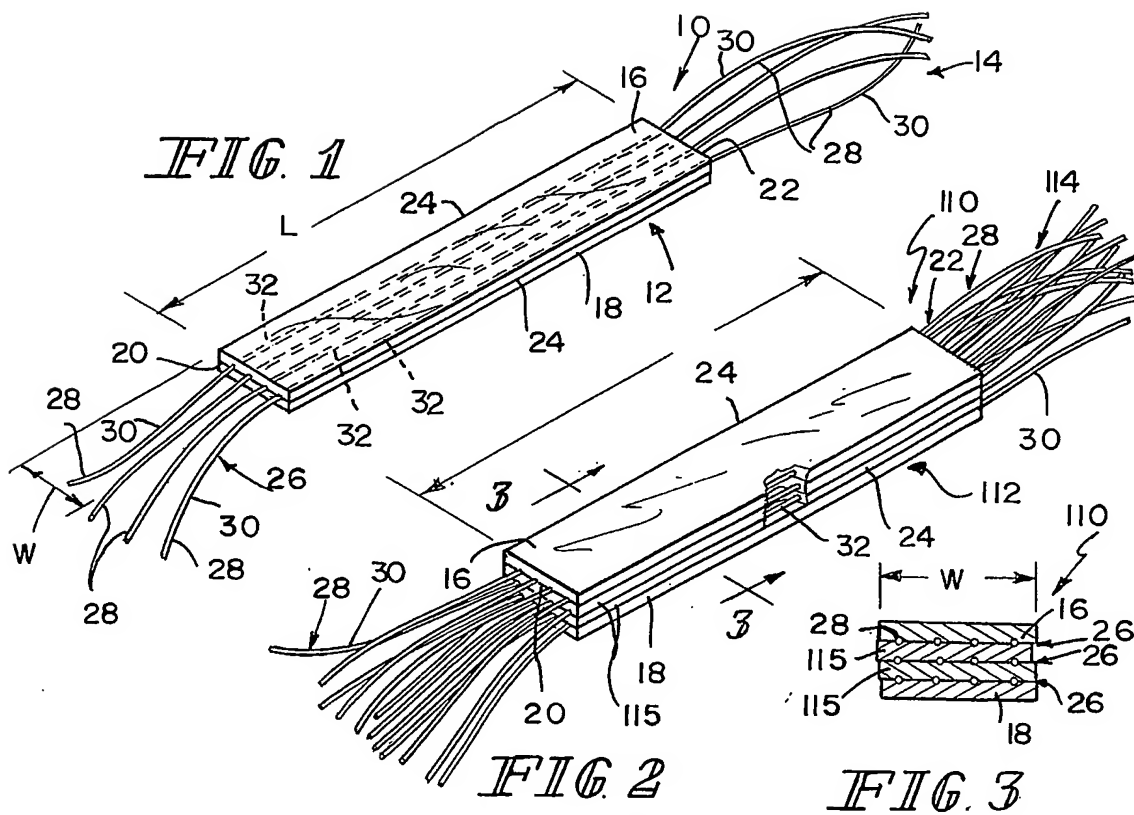
25 25. The method of claim 20, further comprising the step of sculpting the foam.

26. The method of claim 20, wherein the polymer solution is selected from the group consisting of PCL, PLA, PGA, PDO, TMC, PVA, copolymers thereof, and blends thereof.

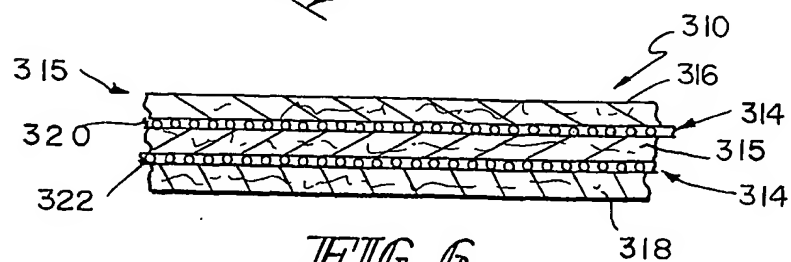
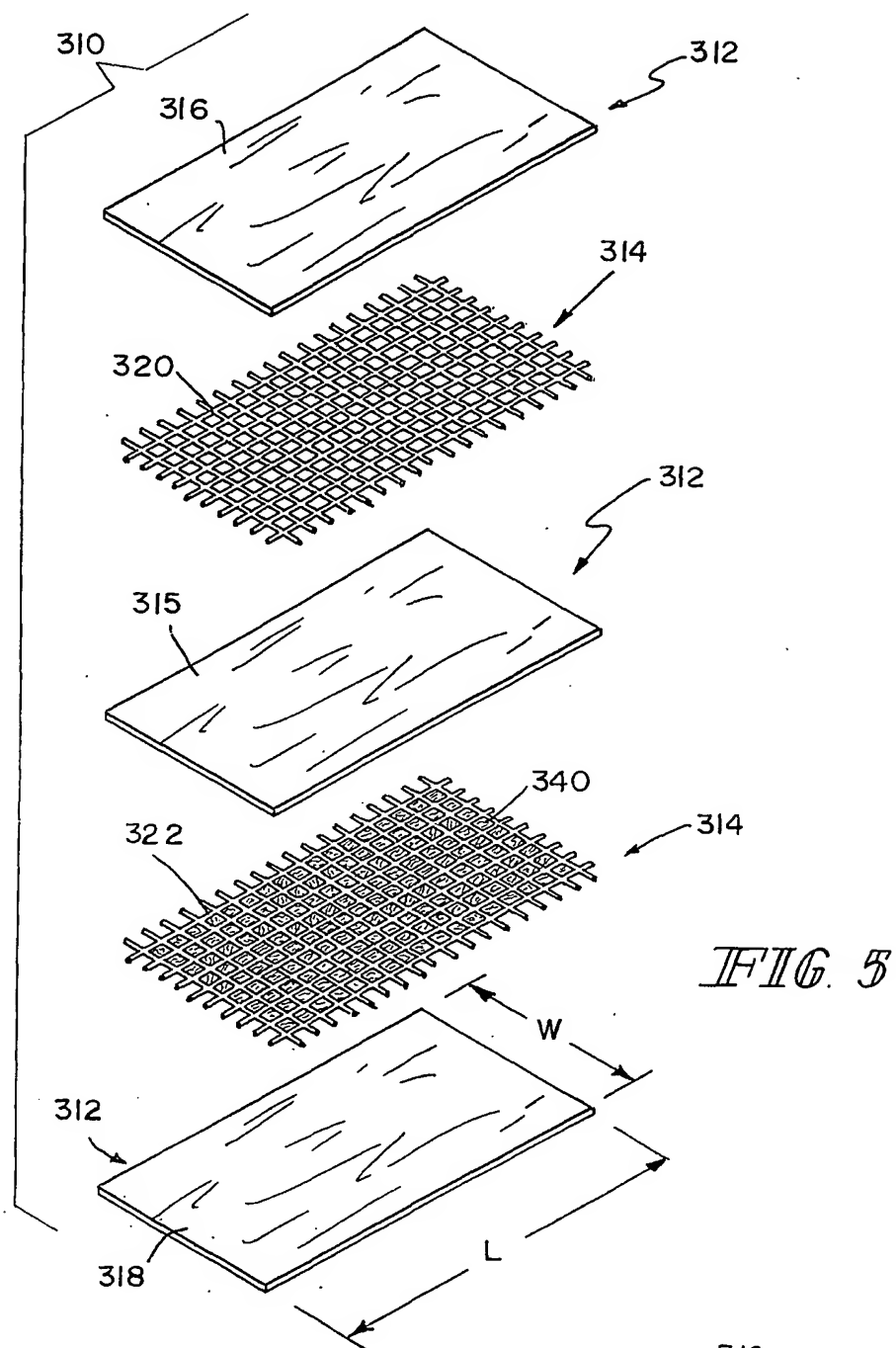
27. The method of claim 20, further comprising the step of placing the layer of ECM material and the polymer solution into a mold prior to
30 lyophilization.

28. The device made according to claim 20.

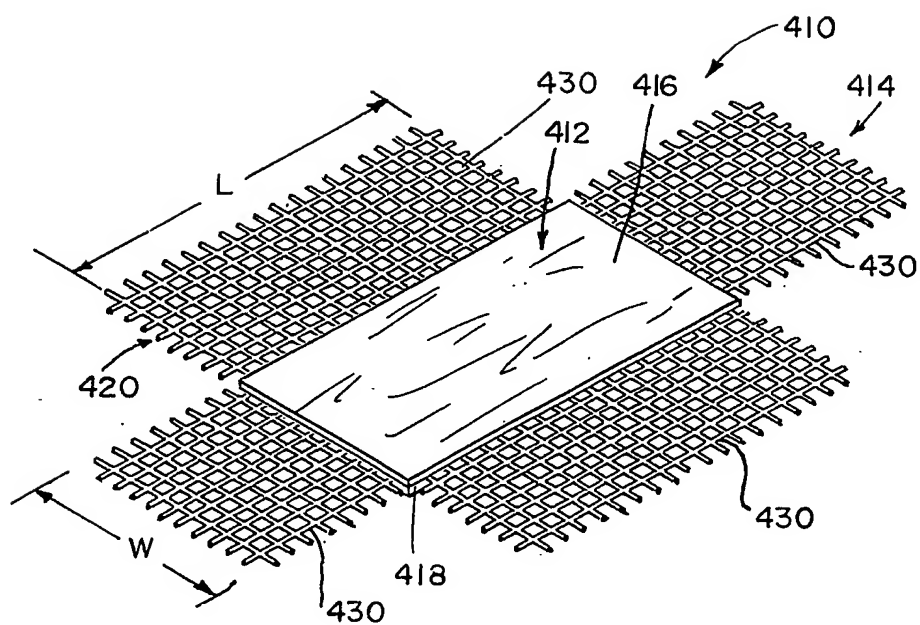
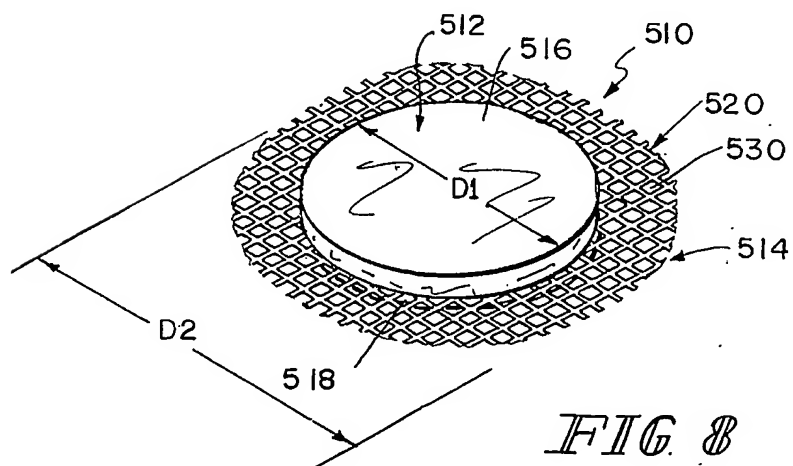
1/5



2/5



3/5

*FIG. 7**FIG. 8*

4/5

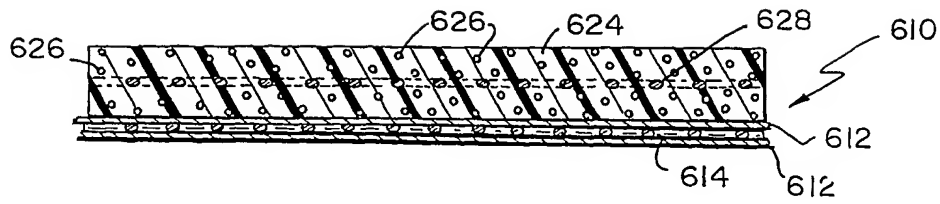


FIG. 9

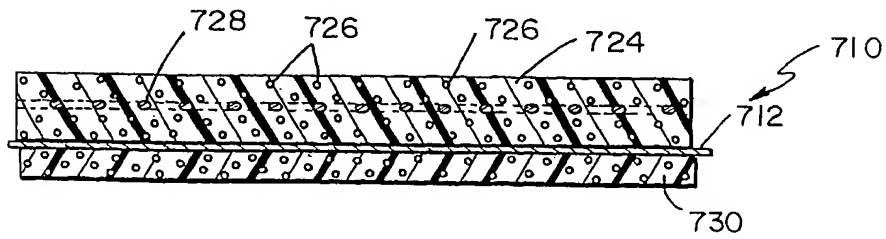


FIG. 10

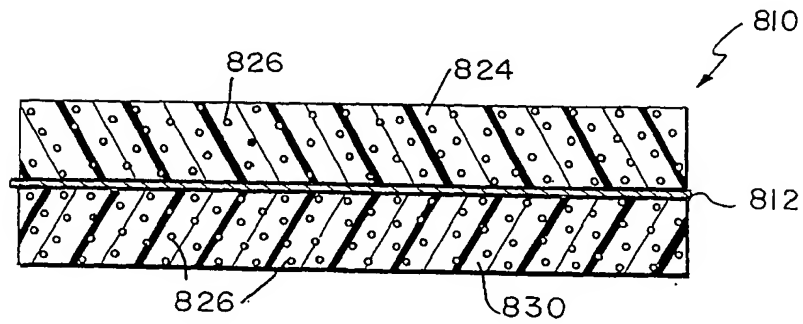
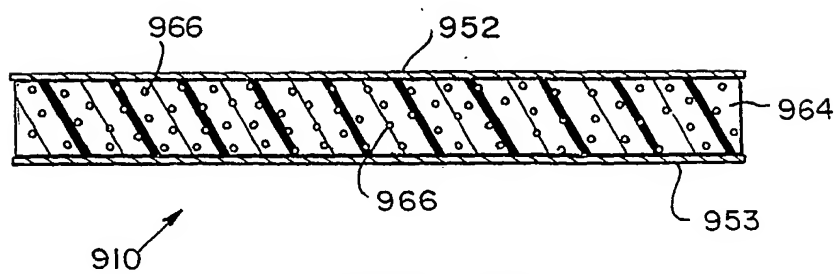
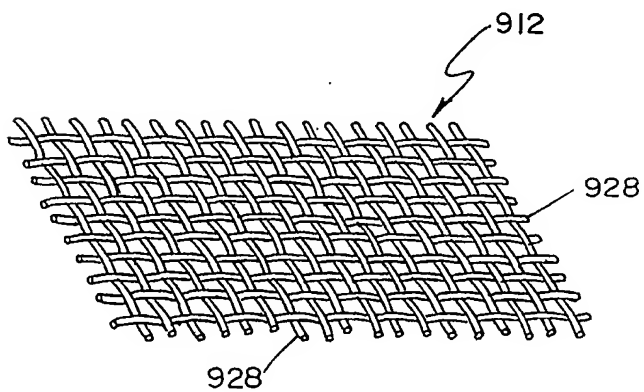


FIG. 11

5 / 5

*FIG 12**FIG 13*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/22364

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 2/02
US CL : 623/23.72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 623/23.72, 23.75, 23.76

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST TEXT SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,759,205 A (Valentini) 02 June 1998 (02.06.1998), see col. 5, lines 42-60 and col. 6, lines 17-29.	1, 19, 20 and 28
A	US 6,409,764 B1 (White et al) 25 June 2002 (25.06.2002), see entire document.	1-28
A	US 6,176,880 B1 (Plouhar et al) 23 January 2001 (23.01.2001), see entire document.	1-28
A	US 5,855,613 A (Anianavich et al) 05 January 1999 (05.01.1999), see col. 7, lines 62-65; col. 25, lines 55-66 and col. 26, lines 1-14	1-28
A	US 5,591,234 A (Kirsch) 07 January 1997 (07.01.1997), see entire document.	1-22

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" Inter document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search

07 August 2002 (07.08.2002)

Date of mailing of the international search report

04 DEC 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Corrine McDermott

Telephone No. 703-308-0858

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☒ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.